Cetuximab in metastatic squamous cell cancer of the skin: A Swiss case series

Conen, Katrin L ; Fischer, Natalie ; Hofbauer, Günther F L ; Shafaeddin-Schreve, Bahar ; Winterhalder, Ralph ; Rochlitz, Christoph ; Zippelius, Alfred

Abstract: Background: There is current evidence that non-melanoma skin cancers can be successfully treated with cetuximab. Objective: To evaluate the use and efficacy of cetuximab (with or without radiotherapy) in a series of previously treated patients with metastatic squamous cell cancer of the skin (SCCS) in Switzerland. Methods: We performed a retrospective analysis of six patients from four centers. Endpoints were disease control rates (DCRs) at 4-8 weeks, 12-14 weeks and 20-36 weeks of treatment. Treatment-related toxicity was evaluated additionally. Results: A median of 14 cycles of cetuximab were applied. DCR was 67% at 4-8 weeks, 50% at 12-14 weeks and 33% at 20-36 weeks. In 4-8 weeks responders, mean relapse-free time was 12 ± 6.2 months and mean overall survival was 25 ± 16.2 months. Grade I-III acne-like rash developed around week 3 of treatment in 83%. Conclusions: Cetuximab treatment in patients with metastatic SCCS achieved an overall DCR of 67% at 4-8 weeks of treatment. This study underlines the current evidence that SCCS can be successfully treated with cetuximab. Introduction In Switzerland, squamous cell cancer of the skin (SCCS) and basal cell cancer are the most common cutaneous cancers with no less than 15,000 estimated new cases diagnosed per year [1]. The median age at diagnosis of SCCS is 70 years [2]. Most patients with primary SCCS have an excellent prognosis due to the possibility of local treatment leading to long-term disease control. High-risk groups for SCCS such as organ transplant recipients or chronic lymphatic leukemia patients are vitally threatened [3,4]. In patients with metastatic disease, long-term overall survival rates are <20% for patients with local lymph node metastases and <10% for patients with distant metastases (mainly involving the lungs, brain, liver, skin and bones) [2]. The treatment of advanced-stage SCCS is challenging as surgical excision becomes impossible. Few therapeutic options are available and the evidence supporting their use is based mainly on non-randomized trials [5,6]. Cisplatin-based chemotherapeutic regiments have short-term efficacies with an overall response rate of up to 80% in locally advanced SCCS [5,6]. However, the severe toxic side effects associated with these regimens limit their use in elderly patients, who make up the majority of cases of SCCS. Alternative treatment options are clearly needed. The epidermal growth factor receptor (EGFR) is a membrane-bound tyrosine kinase receptor that is highly expressed in normal epidermal keratinocytes, many epithelial tumors and in particular SCCS [7,8]. EGFR expression in SCCS shows no mutations or loss of expression as in other tumors [8]. EGFR is activated by ligand binding and receptor dimerization which subsequently activates multiple downstream pathways involved in cell proliferation and survival [7]. Cetuximab is an anti-EGFR monoclonal antibody that has been approved for the treatment of squamous cell cancer of the head and neck and colorectal cancer. In a published phase II trial, single-agent cetuximab demonstrated promising clinical activity in treatment-naïve patients with unresectable, locally advanced SCCS, achieving an overall disease control rate (DCR) of 69% and a response rate of 28% [9]. Several retrospective single case reports and case series have described the effects of cetuximab in both treatment-naïve and multiply pretreated patients with metastatic SCCS [10,11,12,13,14,15]. A recently published summary of 54 cases of locally advanced and metastatic SCCS treated with cetuximab reported a 30% partial response and a 18.5% complete response in these patients [15]. Overall, pretreated patients seemed to benefit less than previously untreated patients. Since the clinical efficacy of cetuximab in colorectal tumors and squamous cell cancer of the head and neck has

been correlated with early development of acne-like skin rash, the predictive role of skin rash in patients with SCCS treated with cetuximab deserves further study [9,15]. The main objective of this study was to review the use, efficacy and toxicity of cetuximab in a series of previously treated patients with metastatic SCCS in Switzerland in the context of the published literature. Methods Patient records from four participating centers in Switzerland were retrospectively reviewed to identify individuals who presented with disease progression after any previous therapy of metastatic SCCS and who were treated with cetuximab between 2010 and 2012. We collected baseline data from the patients' records using a standardized questionnaire as described below. The primary study endpoint was the DCR at 4-8 weeks, 12-14 weeks and 20-36 weeks of treatment. Moreover, relapse-free time under cetuximab treatment, i.e. the time between cetuximab treatment start and disease progression, as well as overall survival at the time of final data analysis was evaluated. We also examined treatment-related side effects and their correlation with disease control. As all data were collected as part of routine diagnosis and treatment, no ethical approval was required. Questionnaire To guide collection of baseline data from records by the physicians, a questionnaire including demographic data as well as personal and medical factors was used. Other characteristics recorded included the date of first disease presentation, pathological status, interventions, medications, control rates, dose and duration of cetuximab, adverse events that were judged to have been caused by cetuximab and overall health status (Eastern Cooperative Oncology Group [ECOG] performance status). Cetuximab-related adverse events were classified according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 3.0). Tumor response (complete response, partial response) was assessed every 2-3 month until disease progression according to RECIST (version 1.1.) criteria in computed tomography or magnetic resonance imaging [16]. Statistics Statistical analysis was performed using the Excel software program (version 2010). Analyses were performed for the entire patient cohort and percentages and descriptive statistics were used to summarize the data. Results Baseline Characteristics Six patients with previously treated metastatic SCCS were identified who received cetuximab between 2010 and 2012. As listed in table 1, the median age of the patient population was 77 ± 21.8 years. There was a male predominance (67 vs. 33%). Overall, patients received a median of 14 ± 12 cycles of cetuximab (range 3-21). All six patients received a cetuximab loading dose of 400 mg/m2 followed by a weekly dose of 250 mg/m2. After 2-4 weeks, treatment was changed to a two-weekly application of 500 mg/m2 in three of the six patients. The primary tumor was located in the area of the head in four (67%) patients and in the trunk and extremities on one (17%) patient each. All patients suffered from visceral metastases commonly involving the lungs, liver or brain. All patients had previously undergone surgical resection and had been previously treated either with chemotherapy (cisplatin, 5-fluorouracil) or radiotherapy. Two of the six (33%) patients received cetuximab treatment concomitant to radiotherapy. The ECOG performance status of patients at baseline was 0 in two (33%) patients and 1 in four (67%) patients.

DOI: https://doi.org/10.1159/000362384

Original Paper

Dermatology

Dermatology 2014;229:97–101
DOI: 10.1159/000362384

Received: January 20, 2014
Accepted after revision: March 22, 2014
Published online: June 7, 2014

Cetuximab in Metastatic Squamous Cell Cancer of the Skin: A Swiss Case Series

Katrin L. Conen[a] Natalie Fischer[b] Günther F.L. Hofbauer[c]
Bahar Shafaeddin-Schreve[c] Ralph Winterhalder[d] Christoph Rochlitz[a]
Alfred Zippelius[a]

[a]Universitätsspital Basel, Medizinische Onkologie, Basel, [b]Kantonsspital Winterthur, Medizinische Onkologie, Winterthur, [c]Universitätsspital Zürich, Dermatologische Klinik, Zurich, and [d]Kantonsspital Luzern, Medizinische Onkologie, Lucerne, Switzerland

Key Words
Metastatic squamous cell cancer of the skin · Cetuximab · Treatment-related toxicity · Acne-like rash

Abstract
Background: There is current evidence that non-melanoma skin cancers can be successfully treated with cetuximab. ***Objective:*** To evaluate the use and efficacy of cetuximab (with or without radiotherapy) in a series of previously treated patients with metastatic squamous cell cancer of the skin (SCCS) in Switzerland. ***Methods:*** We performed a retrospective analysis of six patients from four centers. Endpoints were disease control rates (DCRs) at 4–8 weeks, 12–14 weeks and 20–36 weeks of treatment. Treatment-related toxicity was evaluated additionally. ***Results:*** A median of 14 cycles of cetuximab were applied. DCR was 67% at 4–8 weeks, 50% at 12–14 weeks and 33% at 20–36 weeks. In 4–8 weeks responders, mean relapse-free time was 12 ± 6.2 months and mean overall survival was 25 ± 16.2 months. Grade I–III acne-like rash developed around week 3 of treatment in 83%. ***Conclusions:*** Cetuximab treatment in patients with metastatic SCCS achieved an overall DCR of 67% at 4–8 weeks of treatment. This study underlines the current evidence that SCCS can be successfully treated with cetuximab.

Introduction

In Switzerland, squamous cell cancer of the skin (SCCS) and basal cell cancer are the most common cutaneous cancers with no less than 15,000 estimated new cases diagnosed per year [1]. The median age at diagnosis of SCCS is 70 years [2]. Most patients with primary SCCS have an excellent prognosis due to the possibility of local treatment leading to long-term disease control. High-risk groups for SCCS such as organ transplant recipients or chronic lymphatic leukemia patients are vitally threatened [3, 4]. In patients with metastatic disease, long-term overall survival rates are <20% for patients with local lymph node metastases and <10% for patients with distant metastases (mainly involving the lungs, brain, liver, skin and bones) [2].

The treatment of advanced-stage SCCS is challenging as surgical excision becomes impossible. Few therapeutic options are available and the evidence supporting their use is based mainly on non-randomized trials [5, 6]. Cisplatin-based chemotherapeutic regiments have short-term efficacies with an overall response rate of up to 80% in locally advanced SCCS [5, 6]. However, the severe toxic side effects associated with these regimens limit their use in elderly patients, who make up the majority of cases of SCCS. Alternative treatment options are clearly needed.

KARGER

E-Mail karger@karger.com
www.karger.com/drm

1018–8665/14/229–0097$39.50/0

Katrin L. Conen, MD
Medical Oncology, University Hospital
Petersgraben 4
CH–4031 Basel (Switzerland)
E-Mail katrin.conen@usb.ch

The epidermal growth factor receptor (EGFR) is a membrane-bound tyrosine kinase receptor that is highly expressed in normal epidermal keratinocytes, many epithelial tumors and in particular SCCS [7, 8]. EGFR expression in SCCS shows no mutations or loss of expression as in other tumors [8]. EGFR is activated by ligand binding and receptor dimerization which subsequently activates multiple downstream pathways involved in cell proliferation and survival [7]. Cetuximab is an anti-EGFR monoclonal antibody that has been approved for the treatment of squamous cell cancer of the head and neck and colorectal cancer. In a published phase II trial, single-agent cetuximab demonstrated promising clinical activity in treatment-naïve patients with unresectable, locally advanced SCCS, achieving an overall disease control rate (DCR) of 69% and a response rate of 28% [9]. Several retrospective single case reports and case series have described the effects of cetuximab in both treatment-naïve and multiply pretreated patients with metastatic SCCS [10–15]. A recently published summary of 54 cases of locally advanced and metastatic SCCS treated with cetuximab reported a 30% partial response and a 18.5% complete response in these patients [15]. Overall, pretreated patients seemed to benefit less than previously untreated patients. Since the clinical efficacy of cetuximab in colorectal tumors and squamous cell cancer of the head and neck has been correlated with early development of acne-like skin rash, the predictive role of skin rash in patients with SCCS treated with cetuximab deserves further study [9, 15].

The main objective of this study was to review the use, efficacy and toxicity of cetuximab in a series of previously treated patients with metastatic SCCS in Switzerland in the context of the published literature.

Methods

Patient records from four participating centers in Switzerland were retrospectively reviewed to identify individuals who presented with disease progression after any previous therapy of metastatic SCCS and who were treated with cetuximab between 2010 and 2012. We collected baseline data from the patients' records using a standardized questionnaire as described below. The primary study endpoint was the DCR at 4–8 weeks, 12–14 weeks and 20–36 weeks of treatment. Moreover, relapse-free time under cetuximab treatment, i.e. the time between cetuximab treatment start and disease progression, as well as overall survival at the time of final data analysis was evaluated. We also examined treatment-related side effects and their correlation with disease control. As all data were collected as part of routine diagnosis and treatment, no ethical approval was required.

Questionnaire

To guide collection of baseline data from records by the physicians, a questionnaire including demographic data as well as personal and medical factors was used. Other characteristics recorded included the date of first disease presentation, pathological status, interventions, medications, control rates, dose and duration of cetuximab, adverse events that were judged to have been caused by cetuximab and overall health status (Eastern Cooperative Oncology Group [ECOG] performance status). Cetuximab-related adverse events were classified according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 3.0). Tumor response (complete response, partial response) was assessed every 2–3 month until disease progression according to RECIST (version 1.1.) criteria in computed tomography or magnetic resonance imaging [16].

Statistics

Statistical analysis was performed using the Excel software program (version 2010). Analyses were performed for the entire patient cohort and percentages and descriptive statistics were used to summarize the data.

Results

Baseline Characteristics

Six patients with previously treated metastatic SCCS were identified who received cetuximab between 2010 and 2012. As listed in table 1, the median age of the patient population was 77 ± 21.8 years. There was a male predominance (67 vs. 33%). Overall, patients received a median of 14 ± 12 cycles of cetuximab (range 3–21). All six patients received a cetuximab loading dose of 400 mg/m^2 followed by a weekly dose of 250 mg/m^2. After 2–4 weeks, treatment was changed to a two-weekly application of 500 mg/m^2 in three of the six patients. The primary tumor was located in the area of the head in four (67%) patients and in the trunk and extremities on one (17%) patient each. All patients suffered from visceral metastases commonly involving the lungs, liver or brain. All patients had previously undergone surgical resection and had been previously treated either with chemotherapy (cisplatin, 5-fluorouracil) or radiotherapy. Two of the six (33%) patients received cetuximab treatment concomitant to radiotherapy. The ECOG performance status of patients at baseline was 0 in two (33%) patients and 1 in four (67%) patients.

Response and DCRs

At week 4–8, the overall DCR was 67% (four of six patients). One patient (17%) treated with radiotherapy and cetuximab showed complete response, three (50%) patients achieved partial response, and disease progression

Table 1. Baseline characteristics of the six patients with metastatic SCCS

	Mean ± SD	
Age	77±21.8	
Cetuximab doses	14±12	
	n	%
Sex		
Female	2	33
Male	4	67
Primary SCCS location		
Head	4	67
Trunk	1	17
Extremity	1	17
Visceral metastases (lung, liver, brain)	6	100
Previous surgery	6	100
Previous chemotherapy (cisplatin and 5-fluorouracil)	2	33
Previous radiotherapy	4	67
Cetuximab	6	100
Concomitant cetuximab and radiotherapy	2	33
ECOG PS at cetuximab start		
0	2	33
1	4	67

PS = Performance status.

was recorded in the remaining two patients (table 2). The DCR was 50% (three patients) at weeks 12–14 and 33% (two patients) at weeks 20–36. The patient achieving complete response after 4 weeks of treatment remained a complete responder by the end of the study. Additionally, one patient who achieved partial remission by the first assessment at week 4–8 maintained it by the last assessment status at weeks 20–36. Therefore, two of the six treated patients (33%) were still receiving cetuximab and showing disease control at the time of study evaluation (table 2).

Relapse-Free Time and Overall Survival

Mean relapse-free time in the total study patients was 6 ± 7.2 month. In the four cetuximab responders at 4–8 weeks, mean relapse-free time was 12 ± 6.2 month (table 3). At the time of final study analysis, total overall survival was 12 ± 14.9 month, while two patients were still alive. In the responders-only patient group after 4–8 weeks of treatment with cetuximab, mean overall survival at the time of final analysis was 25 ± 16.2 month (table 3).

Table 2. Response and DCRs

Variable	Response at weeks		
	4–8	12–14	20–36
Complete response	1 (17%)	1 (17%)	1 (17%)
Partial response	3 (50%)	1 (17%)	1 (17%)
Stable disease	0 (0%)	1 (17%)	0 (0%)
Progressive disease	2 (33%)	1 (17%)	1 (17%)
DCR	67	51	33

Table 3. Relapse-free time and overall survival (mean ± SD)

Variable	Months
Mean relapse-free time	
Total (n = 6)	6±7.2
Responders at 4–8 weeks (n = 4)	12±6.2
Overall survival at time of final analysis	
Total (n = 6; 2 still alive)	12±14.9
Excluding patients alive (n = 4)	10±8.9
Responders at 4–8 weeks (n = 4; 2 still alive)	25±16.2

Table 4. Treatment-related adverse events

Adverse event category	All grades		Grades 3 and 4	
	n	%	n	%
Any	6	100	3	50
Acne-like rash	5	83	3	50
Xerosis	2	33	0	0
Paronychia	1	17	0	0
Infection	1	17	0	0
Eye disorder[1]	2	33	0	0

[1] Eye disorder includes conjunctivitis, eye dryness and blepharitis.

Table 5. Correlation of acne-like rash and response rate at 4–8 weeks

Variable	Response		Rash	
	n	%	n	%
Complete response	1	17	1	100
Partial response	3	50	3	100
Stable disease	0	0	0	0
Progressive disease	2	33	1	50

Treatment-Related Side Effects and Association of Acne-Like Rash with Disease Control

The adverse reactions observed during therapy are outlined in table 4. Treatment-related side effects, mainly affecting the skin, were observed in all six patients. One 85-ear-old patient developed a serious adverse event as a severe infection leading to death. Grade I–III acne-like rash developed in five (83%) patients around week 3 of treatment (table 4). All four patients who had their disease controlled at 4–8 weeks showed an acne-like rash, and one patient had a rash without disease control (table 5).

Discussion

When metastatic SCCS requires systemic palliation, treatment with conventional chemotherapy, such as cisplatin, is often precluded by patient age or medical comorbidities [17]. This study underlines the evidence that non-melanoma skin cancers can be successfully treated with cetuximab. Disease control was observed in four (67%) of our patients by treatment week 4–8 with a mean relapse-free time of 6–12 months in these patients. A phase II trial of 36 treatment-naïve patients with unresectable SCCS documented a comparable result, with a DCR of 69% at 6 weeks [9]. There are a number of published single cases and case series reports of recurrent or advanced SCCS treated successfully with cetuximab, consistent with our data [10–14, 18, 19]. Together, they show an overall complete response of 18.5% (17% at 4–8 weeks in our case series) and partial response of 29.6% (50% at 4–8 weeks in our case series) [15]. These observations should encourage a prospective randomized trial of cetuximab therapy in advanced or recurrent SCCS.

Compared to cisplatin-containing chemotherapy, cetuximab is generally well tolerated, with the exception of a notably high incidence of infectious events (total of 36%), which were observed mainly in older patients (83% of all infections in patients >70 years) [9]. In our study we also observed a major infectious complication in an 85-year-old patient leading to sepsis and death after three doses of cetuximab. Infectious complications in patients receiving cetuximab in the context of metastatic head and neck cancer showed no overall increase in infections. However, older head and neck cancer patients >70 years of age using cetuximab showed up to 33% more infections during 1 year under treatment [20]. This is a severe and important observation. We suggest that particular attention should be given to elderly patients receiving cetuximab.

The most commonly experienced side effect was acne-like skin rash, occurring in five of the six patients (83%). Skin rash is an early and well-known side effect of cetuximab treatment and has been reported in 67–77% of cetuximab-treated patients in prior studies in the same treatment setting [10–14, 18, 19]. In the phase II study of 36 treatment-naïve patients with unresectable SCCS, patients who developed acne-like skin rash of any grade at treatment week 6 tended to have improved mean overall survival compared with patients without rash (8.9 vs. 4 months, respectively; $p = 0.054$) [9]. This emphasizes the potential for acne-like rash to predict better tumor response to cetuximab in patients with SCCS, as demonstrated in studies of patients with colorectal and squamous cell cancer of the head and neck [21, 22]. In our patient population we observed that all patients who achieved disease control at 4–8 weeks showed acne-like rash, which might be interpreted in this context.

Though several Swiss centers contributed to our analysis, the main limitations of this study are the small number of cases and the retrospective study design. This case series reports an increased use of EGFR inhibitors in metastatic SCCS in Switzerland. The efficacy observed in our series is consistent with published data and encourages the use of EGFR inhibitors in our country. This is consistent with the available literature.

Conclusions

Cetuximab treatment in pretreated patients with metastatic SCCS achieved an overall DCR of 67% at 4–8 weeks of treatment. One of the six included patients achieved complete response. These data support further investigation of cetuximab in metastatic SCCS and warrant a randomized phase III trial comparing cetuximab with standard chemotherapy in this setting.

Acknowledgements

We would like to thank Beatrice Stüssi from Merck, who helped identify the patients with metastatic SCCS at the participating cancer centers in Switzerland, and Jamie Ashman for editorial assistance with an earlier version of the paper.

References

1 Bulliard JL, Panizzon RG, Levi F: Epidemiology of epithelial skin cancers (in French). Rev Med Suisse 2009;5:882, 884–888.
2 Alam M, Ratner D: Cutaneous squamous-cell carcinoma. N Engl J Med 2001;344:975–983.
3 Hofbauer GF, Freiberger SN, Iotzova-Weiss G, Shafaeddin B, Dziunycz PJ: Organ transplantation and skin – principles and concepts. Curr Probl Dermatol 2012;43:1–8.
4 Hofbauer GF, Anliker M, Arnold A, Binet I, Hunger R, Kempf W, Laffitte E, Lapointe AC, Pascual M, Pelloni F, Serra A; SGDV working group for organ transplant recipients: Swiss clinical practice guidelines for skin cancer in organ transplant recipients. Swiss Med Wkly 2009;139:407–415.
5 Sadek H, Azli N, Wendling JL, Cvitkovic E, Rahal M, Mamelle G, Guillaume JC, Armand JP, Avril MF: Treatment of advanced squamous cell carcinoma of the skin with cisplatin, 5-fluorouracil, and bleomycin. Cancer 1990; 66:1692–1696.
6 Denic S: Preoperative treatment of advanced skin carcinoma with cisplatin and bleomycin. Am J Clin Oncol 1999;22:32–34.
7 Salomon DS, Brandt R, Ciardiello F, Normanno N: Epidermal growth factor-related peptides and their receptors in human malignancies. Crit Rev Oncol Hematol 1995;19:183–232.
8 Dziunycz PJ, Lazarova Z, Duncan N, Wong S, Neuburg M, Hofbauer GF, Olasz EB: EGFRvIII expression in squamous cell carcinoma of the skin. JAMA Dermatol 2013;149: 1240–1242.
9 Maubec E, Petrow P, Scheer-Senyarich I, Duvillard P, Lacroix L, Gelly J, Certain A, Duval X, Crickx B, Buffard V, Basset-Seguin N, Saez P, Duval-Modeste AB, Adamski H, Mansard S, Grange F, Dompmartin A, Faivre S, Mentré F, Avril MF: Phase II study of cetuximab as first-line single-drug therapy in patients with unresectable squamous cell carcinoma of the skin. J Clin Oncol 2011;29:3419–3426.
10 Bauman JE, Eaton KD, Martins RG: Treatment of recurrent squamous cell carcinoma of the skin with cetuximab. Arch Dermatol 2007;143:889–892.
11 Suen JK, Bressler L, Shord SS, Warso M, Villano JL: Cutaneous squamous cell carcinoma responding serially to single-agent cetuximab. Anticancer Drugs 2007;18:827–829.
12 Arnold AW, Bruckner-Tuderman L, Zuger C, Itin PH: Cetuximab therapy of metastasizing cutaneous squamous cell carcinoma in a patient with severe recessive dystrophic epidermolysis bullosa. Dermatology 2009;219:80–83.
13 Rubió Casadevall J, Graña-Suárez B, Hernandez-Yagüe X, Vayreda Ribera J, Huc Grasa O, Brunet Vidal J: Xeroderma pigmentosum: neck lymph node metastasis of a squamous cell carcinoma of the skin treated with cetuximab. Eur J Dermatol 2009;19:163–165.
14 Miller K, Sherman W, Ratner D: Complete clinical response to cetuximab in a patient with metastatic cutaneous squamous cell carcinoma. Dermatol Surg 2010;36:2069–2074.
15 Wollina U: Cetuximab in non-melanoma skin cancer. Expert Opin Biol Ther 2012;12: 949–956.
16 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–247.
17 Wollina U: Nonmelanoma skin cancer on the rise. J Cutan Aesthet Surg 2012;5:11.
18 Kim S, Eleff M, Nicolaou N: Cetuximab as primary treatment for cutaneous squamous cell carcinoma to the neck. Head Neck 2011;33: 286–288.
19 Giacchero D, Barrière J, Benezery K, Guillot B, Dutriaux C, Mortier L, Lacour JP, Thyss A, Peyrade F: Efficacy of cetuximab for unresectable or advanced cutaneous squamous cell carcinoma – a report of eight cases. Clin Oncol (R Coll Radiol) 2011;23:716–718.
20 Lee CC, Ho HC, Hsiao SH, Huang TT, Lin HY, Li SC, Chou P, Su YC: Infectious complications in head and neck cancer patients treated with cetuximab: propensity score and instrumental variable analysis. PLoS One 2012;7:e50163.
21 Bonner JA, Ang K: More on severe cutaneous reaction with radiotherapy and cetuximab. N Engl J Med 2007;357:1872–1873; author reply 1873.
22 Petrelli F, Borgonovo K, Barni S: The predictive role of skin rash with cetuximab and panitumumab in colorectal cancer patients: a systematic review and meta-analysis of published trials. Target Oncol 2013;8:173–181.